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10/593,596	07/27/2007	Ellen D Jorgensen	VTOB.302NP	9085

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/593,596	JORGENSEN ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-11* is/are rejected.

7)☒ Claim(s) *1-4 and 6-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/16/2009, 6/2/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I and the NM_003900 sequestosome 1, claims 1-20, in the reply filed on 9/16/2009 is acknowledged.

Claims 21-52 drawn to non-elected inventions have been canceled.

Claims 5, and 12-20 have been canceled.

Claims 1-4, 6-11 are pending and being examined.

Priority

The instant application is a national stage entry PCT/US05/10733 filed 3/29/2005, which calms priority to provisional application 60/557,929 filed 3/30/2004.

Specification

2. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

3. The presence of NM_003900 in pending claim1 indicates that this is essential matter for the claimed invention (37 CFR 1.57(c)). The presence of NM_003900 in the claim 18 as originally filed provides intent to incorporate by reference.

4. The presences of AK054816, NM_005345, NM_003330, NM_002133, and NM_000963 in claim 11 indicate this is essential matter for the claimed invention. The presence of the accession numbers in claim 18 as originally filed indicates intent to incorporate by reference.

5. The attempt to incorporate subject matter into this application by reference to accession number of GenBank is ineffective because the specification as filed does not specifically recite the root words of “incorporate” and "reference" with respect to the claimed accession number as required by 37 CFR 1.57 (b). An attempt to correct this improper incorporation by reference objection, should amend the specification to specifically recite that the claimed GenBank accession is incorporated by reference, add the sequence to the sequence listing, identify in the specification the accession is the SEQ ID NO, and demonstrate the sequence incorporated by reference was uniquely identified at the time of filing by the accession number.

Claim Objections

6. Claims 1-4, 6-11 are objected to because of the following informalities: Claims 1, 8, 9, and 10 recite the limitations “said first population,” “said second population,” "said first and second populations". Claim 1 recites, “a first isolated population of cells” in step C and “a second isolated population of cells” in step g. The claims appear be using the "first isolated population" and "second isolated population" for antecedent

basis. It is suggested that the claims be amended such that a clear nexus between the "said first population" and "said second population" can more clearly be made by either adding isolated to the "said." All dependent claims are objected as they have all the limitations of the claims from which they depend.

7. . Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4, 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction

or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Claim 1 is drawn to methods of making a tobacco product that comprising:

(a) providing a first tobacco product;

(b) obtaining smoke from said first tobacco product;

(c) contacting a first isolated population of cells with said smoke;

(d) measuring the level of expression of

NM 003900 Sequestosome 1 in said first population of cells in response to said contact with said smoke from said first tobacco product;

(e) providing a second tobacco product; that has been modified to reduce;

(f) obtaining smoke from said second tobacco;

(g) contacting a second isolated population of cells with said smoke from said second tobacco product;

(h) measuring the level of expression of NM 003900 Sequestosome 1 in said second population of cells, in response to said contact with said smoke or from said second tobacco; and

(i) comparing the level of expression of NM 003900 Sequestosome 1 in said first population of cells measured in step (d) with the level of expression of NM 003900 Sequestosome 1 in said second population of cells measured in step (h); and (j)

selecting the tobacco product that has a reduced expression of NM 003900 Sequestosome 1.

Claim 1 is thus drawn making a tobacco product but has no active step in which a tobacco product is made.

Further claim 1 is drawn to contact "any" cells with "any" smoke from "any" tobacco product and detecting any gene that is broadly identified by NM 003900 Sequestosome 1.

Claim 2 draws the first and second tobacco product to burley tobacco.

Claim 3 draws the first and second tobacco product to flue tobacco.

Claim 4 draws the second tobacco product to a modified tobacco.

Claim 6 draws the first and second tobacco products to cigarettes.

Claim 7 draws the invention of claim 6 to cigarettes that have a filter.

Claim 8 draws the invention to first and second cell populations from normal human cells of the mouth, lung, or tongue.

Claim 9 draws the invention to the use of first and second population of cells being normal human epithelial cells.

Claim 10 draws the invention to detection of the expression level of a second gene in the two cell populations contacted with smoke.

Claim 11 draws the second gene of claim 11 to AK054816 Ferritin heavy_ polypeptide, NM 005345 Heat Shock 70kD protein 1A, NM 003330 Thioredoxin reductase 1, NM 002133 Heme oxygenase (decycling) 1, and NM 000963 Prostaglandin-endoperoxide synthase 2 .

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches a brief transient (15 minute)exposure to smoke alters the transcriptome of NHBE cells growing logarithmically when the expression is examiner 4 and 24 hours post exposure (bottom page 66-tope 67).

The specification teaches that of 21, 329 genes on an array 298 genes were up regulated at both experiments. Of the 298 genes 184 were only up-regulated at the 4 hour post-exposure time point and 69 were exclusively up regulated at the 24 hour time period and 45 were up-regulated at both time periods. The specification teaches 66 genes were down regulated in the experiments, with 35 down regulated exclusively at the 4 hour time period, 30 at the 24 hour time period and 1 down regulated at both time periods. The specification teaches that NM_003900 SQSTM1 sequestome 1 was up regulated 3.34 fold at 4 hours and 2.82 fold at 24 hours, table 10, pages 74.

The specification teaches that quantitative PCR was done to confirm the expression of SQSTM1. However, table 11 teaches the expression of SQSTM1 was 3.9 fold in the microarray experiment, while table 10 teaches it was 3.34 fold increase at 4 hours. Further, the specification in table 11 teaches there was a 2.6 fold increase at 24 in SQSTM1 in the microarray experiment at 24 hours, while table 10 teaches a 2.82 fold increase.

The specification teaches that SQSTm1 is involved in ubiquitination/protein turnover/heat shock (table 12, page 82).

Presence and absence of working examples

The specification fails to provide an example in which a product is made or identified by reduced expression of SQSTM1 or the other genes recited in claim 11.

The state of prior art and the predictability or unpredictability of the art:

Benner et al (Trends in Genetics (2001) volume 17, pages 414-418) teaches that, "Here, the 'homology-implies-equivalency' assumption is restricted to a subset of homologs that diverged in the most-recent common ancestor of the species sharing the homologs. This strategy is useful, of course. But it is likely to be far less general than is widely thought. Two species living in the same space, almost by axiom, cannot have identical strategies for survival. This, in turn, implies that two orthologous proteins might not contribute to fitness in exactly the same way in two species" (see page 414, 3rd column last full paragraph). Benner specifically describes that although the leptin gene homologs have been found in mice and humans, their affect is different (see page 414, 3rd column last paragraph-3rd column page 415). Benner specifically teaches that the leptin gene in mice plays a major role in obesity, but no such effect has been demonstrated in humans due perhaps to the different evolutionary forces. Benner thus teaches that the activity and function of genes in different species is unpredictable.

The art of Cheung et al (Nature Genetics, 2003, volume 33, pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among

individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The level of skill in the art:

The level of skill in the art is deemed to be high

Quantity of experimentation necessary:

MPEP 608.01 (p)[R-2] states that "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention."

The claims recite "NM_003900, ""AK054816", "NM 005345", "NM 003330", "NM 002133, " and "NM 000963.". The recitation of accession numbers constitutes an attempt to incorporate by reference to the accession numbers the subject matter which is contained within the recited GenBank record. This recitation constitutes an improper incorporation by reference of essential material since it is material that is necessary to describe the claimed invention. Essential material may not be incorporated by reference to non-patent publications (MPEP 608.01)(p).

Therefore, the claims are rejected for failure to comply with the enablement requirement because the specification fails to provide essential subject matter for the practice of the claimed invention. This rejection can be overcome by deleting the specific reference to the accession number from the claim.

Further, order to practice the invention as claimed, one would first have to determine if one of skill in the art could make a tobacco product by the claimed method without unpredictable experimentation. The artisan would start be examining the instant specification to determine if the specification teaches a method in which a tobacco product is made by the claimed method. Examination of the specification as detailed above, indicates that the instant specification teaches of method of identifying genes in NHBE cell that are up regulated in response to smoke by microarray analysis, which includes SQSTm1. The specification teaches that this up regulation was verified by PCR analysis. The specification suggest that the instant method can be used to identify genes that are regulated by smoke but does not provide any examples in which a product has been identified by the steps of the claimed invention as having reduced expression of "any" level of "any" SQSTM1 gene. The specification thus has not demonstrated that such a decreased expression has been identified, thus making it unpredictable to make a tobacco product with decreased expression of SQSTM1. It is unpredictable to make a product that has been identified by the method as claimed. A method in which identification is made and a product is subsequently made from the product may over come this issue.

Further the method would be unpredictable to practice in "any" cells from any subject as Benner teaches that gene homologs in different species often have different functions due to different evolutionary pressures of the species. Thus it would be unpredictable to use any cells without prior knowledge that SQSTM1 is present in the cell and has the same function.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Written Description

5. Claims 1-4, 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 1-4, 7-11 encompass any gene that can broadly be identified by the recitation of NM 003900 Sequestosome 1. Claim 11 requires, "AK054816 Ferritin heavy_ polypeptide, NM 005345 Heat Shock 70kD protein 1A, NM 003330 Thioredoxin reductase 1, NM 002133 Heme oxygenase (decycling) 1, and NM 000963 Prostaglandin-endoperoxide synthase 2." The claims do not set forth any structural requirements for the genes or accession numbers claimed.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification provides no sequences to the claimed genes or accession numbers. The specification does not limit "cell population to human cells." Thus the broad recitation of gene names

and accession numbers broadly encompass any nucleic acid that can broadly be encompassed by the gene name or accession number in any species. This is an enormous genus of nucleic acids.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The specification does not set forth any structural limitations for claimed accession numbers or genes.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides no structural limitations for the claimed genes or accession numbers. The claims read in light of the specification encompass any nucleic acid molecule that can broadly be described by the gene name or accession number. This is an enormous genus of nucleic acids.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the

encompassed nucleic acids regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid NM 003900 Sequestosome 1, “AK054816 Ferritin heavy_ polypeptide, NM 005345 Heat Shock 70kD protein 1A, NM 003330 Thioredoxin reductase 1, NM 002133 Heme

oxygenase (decycling) 1, and NM 000963 Prostaglandin-endoperoxide synthase 2" does not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed gene or polymorphisms. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding the claimed gene name and accession numbers is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules claimed. Amendment of the claims to reflect a specific species relative to a specific gene name (without the accession number) or identify the sequences claimed by a SEQ ID NO may allow for this rejection to be withdrawn.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-4, 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 and 6-11indefinite because it lacks a positive active step relating back to the preamble. The preamble recites a method of making a tobacco product,

however the last positive active step is drawn to identifying a tobacco product. The claims as presented lack any step in which a tobacco product is made, but provide steps in which the expression of a specific gene is determined in response to two tobacco products. Therefore it is unclear as to whether the method is drawn to making a tobacco product or identifying a tobacco product. This rejection may be overcome by amending the preamble of claim 1 to indicate the claim is drawn to selecting a tobacco product.

Claim 1 recites, "acid NM 003900 Sequestosome 1." It is unclear if the claim requires a nucleic acid comprising or consisting of the recited GenBank accession number, a fragment of accession number, or any gene that can broadly identified by the gene name in any species. Further if the intent is to require only a portion of the claimed GenBank Accession number it is unclear if the claimed sequence must also be identified by the gene name. Claims 2-4 and 6-11 are rejected as they depend from claim 1.

12. Claim 10 recites the limitation "said whole smoke" in the last line. Neither claim 1 or claim 10 previously recite, "whole smoke." Thus there is insufficient antecedent basis for this limitation in the claim. Further claim 1 requires smoke from two tobacco products. It is unclear if "said whole smoke" is intended to refer to the some from the first of second smoke product. This rejection can easily be overcome by amending claim 10 to recite, "further comprising measuring the level of a second gene in steps d and h of claim 1." Claim 11 is rejected as it depends from claim 10 and thus has all the limitations of claim 10.

Summary

NO claims are allowed

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Examiner, Art Unit 1634

Steven Pohnert